REMARKS

Claims 1-2 and 4-20 are pending in the instant application. Claims 1, 2 and 4-20 have been rejected. Claims 11 and 16-20 have been canceled. Claims 1 and 15 have been amended. Reconsideration is respectfully requested in light of the amendments and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 4-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Forman et al. (US 2002/0132223 A1), in view of Bennett et al. (US Patent 5,998,148) and Baracchini et al. (US Patent 5,801,154). The Examiner suggests that it would have been *prima facie* obvious for one of ordinary skill in the art to make antisense compounds as claimed because the prior art has disclosed inhibition of FXR via antisense or ribozymes as well as teaching the modifications of the claims. Applicants respectfully traverse this rejection.

At the outset, Applicants have amended the claims to recite that the antisense compounds of the instant invention are targeted to a specific nucleobase region within the coding region of human FXR of SEQ ID NO: 3. Support for this amendment can be

found at pages 80-83 of the specification as filed, Table 1, where the specific nucleobase region of the amended claims is taught as a target region for antisense compounds.

Forman et al. disclose the role of FXR in cardiovascular disease and the idea of inhibiting activity of this gene in order to treat disease, including inhibition through the use of antisense compounds or ribozymes. Nowhere does this patent teach or suggest the use of antisense compounds targeted to a specific region of human FXR of SEQ ID NO: 3 as now claimed. Therefore, this primary reference fails to teach or suggest the instant invention as now claimed.

The secondary references cited fail to overcome the deficiencies in teaching of this primary reference.

Bennett et al. disclose the use of antisense compounds to inhibit expression of microtubule-associated protein 4. Although the concept of targeting regions of genes with antisense is discussed, nowhere does this patent teach or suggest the use of antisense compounds targeted to a specific region of human FXR of SEQ ID NO: 3 as now claimed.

Baracchini et al. disclose the use of antisense compounds to inhibit expression of multidrug resistance associated protein.

Again, although the concept of targeting regions of genes with antisense is discussed, nowhere does this patent teach or suggest the use of antisense compounds targeted to a specific region of human FXR of SEQ ID NO: 3 as now claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. A mere teaching of the concept of antisense and the function of a gene does not provide one of skill in the art with the understanding or an expectation of success that inhibition of expression of SEQ ID NO: 3 would occur with antisense oligonucleotides from 8 to 50 nucleobases in length that are targeted to a specific nucleobase region within the coding region of this sequence as now claimed. It is only with the specification in hand that one of skill is able to see how to design antisense that are capable of inhibiting expression of SEQ ID NO: 3. Further, there is no motivation for one of skill to

combine these reference teachings. Therefore, this combination of art fails to establish a *prima facie* case of obviousness. Withdrawal of this rejection is therefore respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 15-20 have been rejected under 35 U.S.C. 112, first paragraph, because the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner suggests that the art of antisense is unpredictable and that the specification lacks adequate guidance for therapeutic applications. Applicants respectfully traverse this rejection.

Applicants disagree with the Examiner's suggestion that the cited references support the position that application of antisense *in vivo* is highly unpredictable or problematic.

The Examiner has pointed to articles concerning the technology of antisense oligonucleotides to support the view that antisense technology is unpredictable and that predicting efficacy based on *in vitro* data is problematic. However, when one reads each of the papers as a whole, as required under MPEP

2141.02, these references actually teach the potential usefulness of this class of drugs in humans, and more importantly fail to provide any reasonable basis to doubt the pharmacological activity observed in cells in the instant invention would also occur in humans. Therefore, what these papers cited by the Examiner actually teach is that antisense oligonucleotides must be developed using well designed studies that progress logically from activity in cells to activity in animals, and then to testing in humans. Nowhere in the references cited do the authors state or suggest that results of well-designed *in vitro* pharmacological studies would not be predictive of activity in humans.

Branch (1998) is cited by the Examiner in support of his position. This paper teaches the need to develop antisense molecules based on sound data and careful screening, data such as are presented in the instant specification. Nowhere does the paper state that extrapolation from *in vitro* data to *in vivo* effects in humans is unpredictable. The Examiner, however, attempts to use this paper to support suggestions concerning the inaccessibility of most potential target RNA binding sites to antisense molecules and the unpredictability of antisense

effects. One of skill in the art would not expect to predict the "winning" antisense compound *a priori*, but would screen a reasonable number of compounds in order to find the one best suited to his or her needs. Time and difficulty of experiments are not determinative of enablement if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.(MPEP 2164.06). The fact that effective antisense drugs are selected from large pools of candidates and then optimized, rather than predicted *a priori*, does not indicate lack of enablement, *i.e.*, the need for undue experimentation. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

The Office Action also cites Branch as supporting the unpredictability of non-antisense effects. The predictability,

or lack thereof, of an effect which is not the claimed invention is irrelevant. One of ordinary skill is well aware of how to use proper controls to elucidate antisense inhibition of a desired target. Branch is also cited as teaching the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available (Page 46, second column). However, as discussed *supra*, the teachings of a reference must be read in its entirety, not only in bits and pieces to support the Examiner's interpretation. See MPEP 2141.02. The full excerpt which has been cited in part by the Examiner begins, "As is true of all pharmaceuticals, the value of a potential antisense drug"... In other words, antisense drugs are no different from any other drugs. If the need for evaluation of dose-response and therapeutic index were a bar to patentability, no drug would be patentable. Clearly this is not the proper standard. Thus nowhere does the reference of Branch teach that one of skill would be unable to use the compounds or methods of the invention in an *in vivo* environment.

The paper by Jen and Gewirtz (2000) is a review paper on the evolution of technology to suppress gene expression, including

antisense technology, and its use in human disease. Nowhere does this paper teach or suggest that antisense compounds identified from well-designed *in vitro* studies would be inherently unpredictable when used *in vivo*.

Further, the Examiner has failed to support the proposition that administration of antisense to FXR would be unpredictable based on any objective evidence. In contrast, data are provided in Example 15 showing the selection and design of antisense oligonucleotides to selected targets and their activity *in vitro*. Therefore, Applicants have clearly met their burden under 112, first paragraph. Further, Applicants respectfully remind the Examiner that the "absence of working examples should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement and the specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation". In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)). (MPEP 2164.02).

However, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 15 and canceled claims

16-20, with Applicants reserving the right to file continuing applications directed to the canceled subject matter. Accordingly, withdrawal of this rejection is respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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